REMARKS

Reconsideration of this application is respectfully requested.

Claims 91-111 were previously pending in this application. In the claim listing above, claims 91 and 105 have been amended, and new claims 112-117 have been added. No claims have been canceled in the claim listing above. Accordingly, claims 91-117 are presented for further examination in this application.

Changes To The Claims

As just indicated, claims 91 and 105 have been amended and new claims 112-117 have been added.

In claim 91, the "sequence or sequences for the viral vector nucleic acid component *have been* stably integrated in the genome of said cell line, . . ." In a similar fashion, "sequences for the non-nucleic acid components of said viral vector *have been* stably integrated in the genome of said cell line and code for envelope genes from two different viruses." At the same time, a phrase ("are introduced into said packaging cell line by transient expression, episomal expression or stably integrated expression") has been deleted from claim 91.

The dependency in claim 105 has been corrected in response to the rejection under 35 U.S.C. §112, 2nd ¶. By changing the dependency from "91" to "99," a proper antecedent basis for "said antisense RNA" has been established.

New claims 112-117 have been added. Like claim 91, claim 112 is independent and is also directed to a packaging cell line for propagating a viral vector independent of a helper virus. In claim 112, the viral vector comprises a nucleic acid component and at least two different non-nucleic components, wherein one of the non-nucleic acid components has a tropism for the cell line and the other non-nucleic acid component has a tropism for a target cell which is different from

non-nucleic acid component has a tropism for a target cell which is different from the cell line. According to claim 112, the nucleic acid component and the non-nucleic acid components are capable of forming a specific complex or complexes, and sequences for the non-nucleic acid components of the viral vector have been stably integrated in the genome of the cell line and code for envelope genes from two different viruses.

A brief mention should be made with respect to the separate subject matter of new claim 112 and amended claim 91. In order to emphasize that the sequences necessary for production of viral vector particles with two separate trophisms are integrated into the chromosome of a packaging cell line, Applicants have added new claim 112 that does not include a description of integrated sequences that will be packaged into vectors. As such, claim 112 represents a packaging cell line that is ready for use, and one that only requires the introduction of a nucleic acid sequence that will be packaged into viral particles. Claim 112 is differentiated from claim 91 which describes a packaging cell line that has the sequence to be packaged already present in the packaging cell of a packaging cell line.

Dependent claim 113-117 depend from claim 112 and they recite similar subject matter as claims 92 and 94-97, the latter depending from claim 91. Thus, claim 113 recites that the viral vector "comprises a retrovirus or retroviral sequences." Claim 114 recites that the packaging cell line and the target cell "are from different species." Claim 115 defines the packaging cell line as being "a non-human animal species and said target cell is human." Claim 116 recites that the "non-human animal species is murine." Claim 117 recites that the target cell "comprises T cells, liver cells, bone marrow cells, epithelial cells, or a combination of any of the foregoing."

It is believed that the subject matter of amended claims 91 and 105, as well as new claims 112-117, is fully supported by Applicants' originally filed disclosure

and that it clarifies the subject matter now being pursued. Entry of both the amendments to claim 91 and new claims 112-117 is respectfully requested.

Before addressing the rejections, Applicants appreciate the indication in the Office Communication (page 10) that the grounds of rejection applied in the previous Office Action have been withdrawn.

The Rejection Under 35 U.S.C. §101

Claims 91-111 stand rejected for non-statutory subject matter under 35 U.S.C. §101. According to the December 19, 2007 Office Communication (page 2):

> Claim 91 appears to be a product claim (a packaging cell) but the claim recites process steps whereby the product appears to be modified. The claim does not appear to be a product by process claim and hence the claim appears to be a product claim and a process claim, which is non-statutory. Claims 92-111 are rejected based upon their dependence upon claim 91.

The rejection for non-statutory subject matter is believed to have been obviated by the above claim amendments and new claims. Whatever process-type language may have been at issue is believed to have been removed from the present claims which conform to packaging cell lines, i.e., compositions of matter.

Reconsideration and withdrawal of the rejection under 35 U.S.C. §101 are respectfully requested.

The First Rejection Under 35 U.S.C. §102

Claims 91-94, 97-98,109, 110 and 111 stand rejected under 35 U.S.C. §102(b) as being anticipated by Strair et al. [Nucleic Acids Research 21:4836-4842 (1993)]. According to the Office Communication (pages 3-5):

Applicants claim a packaging cell line for propagating a viral vector independent of a helper virus, said viral vector comprising a nucleic acid component and at least two different non-nucleic components, wherein one of said non-nucleic acid components has a tropism for said cell line and the other non-nucleic acid component has a tropism for a target cell which is different from said cell line, said nucleic acid component and said non-nucleic acid components being capable of forming a specific complex or complexes, wherein said sequence or sequences for the viral vector nucleic acid component is stably integrated in the genome of said cell line, and said sequence or sequences for the non-nucleic acid components of said viral vector are introduced into said packaging cell line by transient expression, episomal expression or stably integrated expression.

The examiner is interpreting the language of Claim 91 as follows: Claim 91 appears to be a composition claim reading on a packaging cell line. The claim contains intended use language which usually does not carry patentable weight in a composition claim. The claim recites non-nucleic acid properties of the viral vector wherein the recited properties of the viral vector may or may not be imparted to the vector by the packaging cell. For example, the tropism of the viral vector may be imparted after the viral vector is made by the packaging cell, i.e. the viral vector envelope may be conjugated with a compound which determines its tropism. The claim recites a process step which appears to indicate that the packaging cell line is modified (at some point in time) to include sequences which encode the non-nucleic acid components. It is unclear if the results of the process step are intended to be part of the packaging cell line because they are not recited as a product by process but instead as some optional further modification of the claimed cell line.

When the intended use language (i.e. for propagating a viral vector independent of a helper virus...) is removed and the language describing the non-nucleic acid properties of the viral vector is removed and the process steps reciting modifying the packaging cell at some point in time with regard to introducing sequences for the non-nucleic acid components of the viral vector are removed, the claim reads on **a packaging cell wherein the nucleic acid sequence component of the viral vector is stably integrated in the genome of said cell line.** The claims will be

examined based upon this interpretation.

Applicants use the term "derived from" with regard to nucleic acid sequences. Since the metes and bounds of this terminology are not defined (i.e. applicants do not recite the methodologies by which a sequence is derived from another sequence), the examiner interprets this language to mean that a sequence is derived from another sequence if it contains at least one nucleotide in common with the sequence from which it was derived.

Strair et al. (Nucleic Acids Res., 1993, Vol. 21, No. 20, pp. 4836-4842, see whole article, particularly the Abstract, Figs. 1 and 4, pp. 4839-4840) recites a packaging cell line (H9/HIV-gpt or HeLa T4/HIV-LacZ) comprising a viral vector (HIV vector) wherein the nucleic acid component of the vector is stably integrated into the genome of the cell line. The vector can be rescued by supplying the functions missing from the integrated HIV vectors and therefore the cells are packaging cells. The viral vector DNA comprises sequences "derived from" cDNA (i.e. LacZ or gpt gene sequence) wherein said sequences can be expressed in a target cell such as a T cell. Strair et al. therefore teaches the claimed invention.

The first anticipation rejection is respectfully traversed.

In response, Applicants offer the following remarks.

By way of background, previous art has shown the ability to "pseudotype" where a viral backbone from one type of virus is encapsidated by envelope genes from another virus thereby altering the host range of a viral vector. Previous art has also shown that infection of cells with two different kinds of viruses can result in "mosaic" or "hybrid" virions which consist of a mixture of the envelope proteins from each virus, thereby carrying out a more complicated version of pseudotyping. Experiments with transfections of plasmid either as part of cotransfections or by superinfection of a previously infected cell line has also been used to study the generation of such hybrid particles. There is no reference in the art prior to the current filing, however, as to a stable packaging cell line that contains intact env genes from two different viruses enabling a constant and stable source of hybrid

virion packaging elements, thus allowing the user to generate recombinant viral particles wrapped in two different envelope genes. The use of a stable cell line gives superior performance compared to transfections with plasmids or viruses because an intrinsic level of expression of each viral env type can be individually monitored for each isolate that is used to generate a packaging cell line. Thus isolates can be selected that give the optimal ratio of expression for production of hybrid virions as opposed to transiently transfected cultures that will have various levels of env gene production as well as a number of cells that contain only a single type of env gene.

With regard to the comments in the Office Communication (page 3), Applicants believe that the current change in their claim language makes it clear that the properties imparted to the vector are a property of the packaging cell line. Tropism is a property that is chiefly dependent upon the nature of the viral envelope. This is the particular reason that "pseudotyping" methods have been carried out in the past, namely, to alter the tropism of a particular vector to a more desirable target cell type. As now amended, it is clear in the present claims and invention the that the "non nucleic acid components" are stable elements of the packaging cell lines. There is no indication in the presently claimed invention that tropism properties are derived after production of the vector from the packaging cell line.

Applicants respectfully submit that other comments in the Office Communication (page 4) require elimination of an essential part of the present invention, i.e., the non-nucleic acid portion that endowed dual tropisms. In light of the changes that have been made in claim 91 and the subject matter presented in claim 112, it should be understood that the sequences for the non-nucleic acid portion is now stipulated to be a stable part of the packaging cell line.

Consequently, Applicants believe that Strair et al. cannot reasonably be said to anticipate the present invention and claims for the following reasons. First, one

skilled in the art would not consider his methods as describing a "packaging cell line." Packaging cell lines usually refer to cells that have the components for packaging present prior to the introduction of a vector. As the Office Communication points out, the Strair document describe a cell line that has integrated vector sequences that are rescued (the technical term that is usually applied to this process) by addition of components for production of viral particles. Although it may be a cell line and eventually viral nucleic acids are packaged into viral particles, this would not be understood to be a "packaging cell line." Second, the present invention and claims now clearly specify that the envelope genes are stably integerated. This is an element altogether missing from Strair's disclosed method. Finally, even when the missing HIV components were added by Strair et al., only the env gene from HIV endowed the resultant viral particle with the tropism that is intrinsic to the HIV envelope. In Strair et al., tropisms are not endowed by any of the other proteins that are synthesized after introduction of the helper virus. This difference is made more clear with the amended language since the claim now requires envelope genes from two different viruses be present in the cell line.

Applicants also respectfully disagree with the comments in the Office Communication (page 4) regarding the interpretation of the phrase "derived from" as being equivalent to a single nucleotide being held in common. This is simply not a valid interpretation with which skilled artisans could reasonably agree. The phrase 'derived from" in the context of the disclosure is given its ordinary meaning. Thus, for instance when nucleic acid sequences of the vector are described as being derived from genomic DNA, it would be understood that a physical piece of genomic DNA was the ultimate source of a fragment that was used to create the vector, or contrariwise, sequence information derived from genomic DNA was used as a source to synthesize a nucleic acid fragment that would be used to create the vector. The assertion that "derived from" is equivalent to a single nucleotide in

effect trivializes the connection between chromosomal DNA and a vector sequence. The same situation exists for sequences derived from cDNA where nucleic acids created by reverse transcription of mRNA afford fragments or information that could be used in building a vector. Differences in such origins can have implications for the use of certain genes. For instance, a gene sequence derived from chromosomal DNA could contain all of its promoters and enhancers and usually consists of a mixture of exons and introns. In contrast, a gene derived from cDNA will represent only transcript sequences and typically have all of the introns spliced out.

In view of the lack of identity in materials elements between the presently claimed invention and cited Strair document, Applicants respectfully request reconsideration and withdrawal of the first anticipation rejection.

The Second Rejection Under 35 U.S.C. §102

Claims 91, 93-98 and 109-111 stand rejected under 35 U.S.C. §102(e) as being anticipated by Flotte et al. (U.S. Patent No. 5,658,776). According to the Office Communication (page 5):

> Applicants' invention is as described above. Additionally, applicants that the packaging cell is from a non-human animal or a murine species.
>
> Flotte et al. (US 5,658,776, issued 8/19/1997, filed 6/7/1995, see whole document, particularly columns 9-13, Example 7 and Claims 1-15) teaches packaging cell lines (which can be human cells such as HeLa cells, A549 cells, etc. or can be from rodents (i.e. murine cells) comprising a AAV vector wherein the nucleic acid component of the vector is stably integrated into the genome of the cell line. The vector can be rescued by supplying the functions required for virion morphogenesis and replication and therefore the cells are packaging cells. The viral vector DNA comprises sequences "derived from" cDNA (i.e. neo gene sequence) wherein said

> sequences can be expressed in a target cell such as a human epithelial cell or other cells infected by AAV. Flotte et al. therefore teaches the claimed invention.

The second anticipation rejection is respectfully traversed.

In response, Applicants respectfully point out that as in the case of the previous rejection involving Strair et al., this second rejection for anticipation now involving Flotte's document is nothing more than a description for rescuing viral sequences and it is not a description of a packaging cell line, as set forth in the present claims. Again, in common with the Strair document, only a single viral type (AAV) is used in Flotte et al. for providing the envelope proteins for the resultant viral particle.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the second anticipation rejection.

Commonality of Ownership

Applicants confirm that the subject matter of the various claims was commonly owned at the time any inventions covered therein was made.

The First Rejection Under 35 U.S.C. §103

Claims 99-102 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Flotte et al. (U.S. Patent No. 5,658,776) in view of Chatterjee et al. (U.S. Patent No. 5,474,935). According to the Office Communication (pages 6-7):

> Applicants claim the packaging cell line and viral vector as defined in the above 35 USC 102 rejections. Additionally, applicants recite that the viral vector encodes for an antisense RNA targeted against a mRNA coding for an undesirable protein in a target cell as well as a sequence coding for a protein of interest.
>
> Flotte et al. is applied as above. Flotte et al. does not teach

expression of antisense sequences by viral vectors but indicates that AAV vectors have been used to express antisense sequences in the prior art.

Chatterjee et al. (US 5,474,935, issued 12/12/1995, see whole document, particularly Claims 1-11, columns 8-12, etc.) teaches the use of AAV vectors to express antisense RNAs targeted against mRNAs coding for undesirable proteins (i.e. ICP4 of HSV, etc.) and wherein the vectors can also comprise a gene of interest (i.e. neo gene).

The ordinary skilled artisan, seeking to generate viral vector packaging cells capable of generating AAV vectors capable of expressing an antisense sequence directed against the mRNA from an undesirable gene in a target cell, would have been motivated to combine the teachings of Flotte et al. on the generation of recombinant AAV vector packaging cells with the teachings of Chatterjee et al. on the AAV vectors and packaging cells which generate AAV vectors capable of expressing antisense sequences targeted against mRNAs from undesirable genes (i.e. ICP4 form HSV) in target cells because the expression of antisense sequences targeted against undesirable genes in target cells has been a well known technique to inhibit the growth of undesirable target cells or inhibit virus replication, etc. It would have been obvious for the ordinary skilled artisan to do this because use of viral (AAV) vectors to deliver antisense sequences to target cells, in the context of treatment of diseases, was well known in the art (see Chatterjee et al.) and was a standard use of AAV vectors. Given the teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

The first obviousness rejection is respectfully traversed.

In response, it is respectfully submitted that the addition of Chatterjee's patent to the previously cited Flotte patent does not render the present invention obvious. As discussed earlier in regard to the first anticipation rejection, Flotte et al. do not disclose or suggest a packaging cell line as set forth in the present claims and invention. Combining Flotte's disclosure with Chatterjee's disclosure does not cure the deficiencies of the former.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection.

The Second Rejection Under 35 U.S.C. §103(a)

Claims 103-104 and 106-107 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Flotte et al. (U.S. Patent No. 5,658,776) in view of Chatterjee et al. (U.S. Patent No. 5,474,935) and further in view of Dietz et al. According to the Office Communication (pages 8-9):

> Applicants' invention is as described above. In addition, applicants claim a packaging cell line comprising a viral vector which encodes an antisense RNA targeted against a mRNA coding for an undesirable protein in a target cell and wherein the antisense RNA can be a part of a chimeric RNA molecule that comprises sequences from small nuclear RNAs (for example, U1 snRNA).
>
> Flotte et al. and Chatterjee et al. are applied as above. Neither reference teaches a viral vector which encodes an antisense RNA that can be a part of a chimeric RNA molecule that comprises sequences from small nuclear RNAs (snRNAs).
>
> The ordinary skilled artisan, seeking to develop packaging cell lines capable of generating viral (AAV) vectors capable of expressing an antisense sequence or a chimeric antisense RNA molecule, would have been motivated to combine the teachings of Flotte et al. and Chatterjee et al. on the generation of IAAV packaging cell lines comprising stably integrated AAV vectors capable of expressing antisense sequences targeted against undesirable targets with the teachings of Dietz concerning the use of viral (retroviral) vectors to express chimeric antisense sequences targeted against undesirable genes in target cells because the expression of antisense sequences targeted against undesirable genes was a well known technique in molecule biology and use of viral vectors to deliver chimeric RNAs (comprising antisense and snRNA sequences) to target cells was likewise known and desirable because Dietz teaches that said chimeric RNAs are more stable and more efficacious than non-chimeric RNAs. It would have been obvious for the ordinary skilled artisan to do this because delivery and expression of antisense sequences targeted against undesirable genes had been a well known technique in molecular biology (see Flofte et al. and Chatterjee et al). It would

> further have been obvious for the ordinary skilled artisan to select chimeric RNAs encoding antisense sequences and snRNAs because Dietz teaches that said chimeric RNAs make superior delivery vehicles for delivering the antisense sequences to the target cells. Given the teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

The second obviousness rejection is respectfully traversed.

In response, Applicants respectfully point out that as in the case of the first obviousness rejection, Flotte et al. do not disclose or suggest a packaging cell line as set forth in the present invention and claims. As also discussed in the first obviousness rejection, the addition of Chatterjee's disclosure does not cure the deficiencies in the primary Flotte document. Moreover, the addition of yet another third document to the mix does not overcome Flotte's deficiencies with respect to a packaging cell line.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the second rejection under §103(a).

The Rejection Under 35 U.S.C. §112

Claims 105 and 108 stand rejected for indefiniteness under 35 U.S.C. §112, second paragraph. According to the Office Communication (page 9):

> Claim 105 (and dependent claim 108) are unclear because there is no antecedent basis for the term "said antisense RNA" in claim 91. It is noted that claims 105 and 108 are not rejected under 35 USC 102 or 103(a) because the metes and bounds of the claims cannot be discerned.

The rejection for indefiniteness is believed to have been obviated by the above amendment to claim 105.

In view of the above claim amendment, Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejection against claims 105 and 108.

Favorable action on this application is respectfully urged.

* * * * * *

SUMMARY AND CONCLUSIONS

Claims 91-111 are presented for further examination. Claim 91 has been amended and new claims 112-117 have been added.

The claim fee for adding new claims 112-117 is $150 based upon the presentation of six additional claims above the 21 claims previously paid for (6 X $25 = $150). The Patent and Trademark Office is hereby authorized to charge the requisite $150 claim fee to Deposit Account No. 05-1135. No other fee or fees are believed to be due in connection with this Amendment. If any other fee or fees are due, however, The Patent and Trademark is authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, and to credit any overpayment thereto.

Applicants respectfully submit that all of the instant claims are in allowable condition. Should it be deemed helpful or necessary, the Examiner is respectfully invited to telephone the undersigned at (212) 583-0100 to discuss the subject application.

Respectfully submitted,

Ronald C. Fedus
Registration No. 32,567
Attorney for Applicants

ENZO THERAPEUTICS, INC.
c/o Enzo Biochem, Inc.
527 Madison Avenue, 9th Floor
New York, New York 10017
Tel.: (212) 583-0100
Fax.: (212) 583-0150